# Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States



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## *Maraviroc (Selzentry, MVC)*

**(Last updated December 24, 2019; last reviewed December 24, 2019)**

### Animal Studies

*Carcinogenicity*

MVC was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of MVC in rats showed no drug-related increases in tumor incidence at exposures that were approximately 11 times those observed in humans who received the therapeutic dose.

*Reproduction/Fertility*

No adverse effects were observed on the fertility of male or female rats at doses of MVC that produced exposures (based on area under the curve [AUC]) up to 20-fold higher than those seen in humans given the recommended 300-mg, twice-daily dose.

*Teratogenicity/Adverse Pregnancy Outcomes*

In animal reproduction studies, no evidence of adverse developmental outcomes was observed in animals that received MVC. During organogenesis in the rat and rabbit, systemic exposures to MVC (based on AUC) were approximately 20 times (in rats) and five times (in rabbits) the exposure seen in humans given the recommended 300-mg, twice-daily dose. In a rat prenatal and postnatal development study, maternal MVC AUC was approximately 14 times the exposure seen in humans given the recommended 300-mg, twice-daily dose.[1]

*Placental and Breast Milk Passage*

A study in rhesus macaques showed that single-dose MVC had poor placental transfer and rapid clearance from infant monkeys' blood.[2] Studies in lactating rats indicate that MVC is extensively secreted into rat milk.[1]

### Human Studies in Pregnancy

*Pharmacokinetics*

A U.S./European intensive pharmacokinetic (PK) study measured 12 hour PK profiles in the third trimester and at least 2 weeks postpartum included 18 women who were taking MVC as part of clinical care.[3] Sixty-seven percent of the women in the study were taking MVC 150 mg twice daily with a protease inhibitor; 11% took MVC 300 mg twice daily and 22% took an alternative regimen. The geometric mean ratio for third-trimester AUC versus postpartum AUC was 0.72; the geometric mean ratio for maximum MVC concentration in the third trimester versus maximum MVC concentration postpartum was 0.70. Despite an overall 30% decrease in MVC AUC during pregnancy and a 15% decrease in $C_{trough}$, $C_{trough}$ exceeded the minimum target concentration of 50 ng/mL in all participants except for one woman who had a $C_{trough}$ below 50 ng/mL during both pregnancy and the postpartum period. These data suggest that the standard adult dose adjusted for concomitant antiretroviral (ARV) drugs seems appropriate in pregnancy. A review of interactions between ARV drugs and oral contraceptives found that it is safe to coadminister oral contraceptives with MVC.[4]

*Placental and Breast Milk Passage*

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of MVC.[5] In a study of six mother-infant pairs, the median ratio of MVC concentration in cord blood to MVC concentration in maternal plasma was 0.33 (with a range of 0.03–0.56).[3] Whether MVC is secreted into human milk is unknown.

*Teratogenicity/Adverse Pregnancy Outcomes*

The 30 cases of first-trimester exposure to MVC that have been monitored to date in the Antiretroviral Pregnancy Registry and other available first-trimester exposure data are insufficient to make a risk determination regarding birth defects.[6,7]

*Other Safety Information*

A retrospective study from an English-Irish cohort of 857 pregnant women showed an increased rate of hepatotoxicity among the 492 women who started ARV therapy during pregnancy.[8] MVC, efavirenz, and nevirapine were associated with an increased risk of liver enzyme elevation during pregnancy; the adjusted hazard ratio for MVC was 4.19 (1.34–13.1, $P = 0.01$). In a model that used human placental BeWo cells, MVC inhibited transplacental passage of two fluorescent organic cations, suggesting that it might influence placental drug transfer and cause drug-drug interactions.[9]

**Excerpt from Table 8**

| **Generic Name** (Abbreviation) *Trade Name* | **Formulation** | **Dosing Recommendations**[a] | **Use in Pregnancy** |
|---|---|---|---|
| **Maraviroc** (MVC) *Selzentry* | **MVC (Selzentry)**<br>*Tablets:*<br>• 150 mg<br>• 300 mg | **Standard Adult Dose:**<br>• MVC 300 mg twice daily with or without food<br>• MVC should only be used for patients with CCR5-tropic virus (and no X4-tropic virus).<br>*Dose Adjustments:*<br>• Increase to MVC 600 mg twice daily when used with the potent CYP3A inducers EFV, ETR, and rifampin.<br>• Decrease to MVC 150 mg twice daily when used with CYP3A inhibitors, which includes all PIs except TPV/r and itraconazole.<br>**Pregnancy**<br>*PKs in Pregnancy:*<br>• A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in MVC AUC, but $C_{trough}$ exceeded the recommended minimum concentration of 50 ng/mL.<br>*Dosing in Pregnancy:*<br>• Adjusting the standard adult MVC dose for concomitant use with ARV drugs seems appropriate. | Moderate placental transfer to fetus.[b]<br>No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. |

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

**High:** >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

**Key:** ARV = antiretroviral; AUC = area under the curve; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

## References


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